UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

+ + + + +

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

+ + + + +

MEETING

+ + + + +

TUESDAY,

JANUARY 30, 2001

+ + + + +

The Advisory Committee met at 8:00 a.m., in the Ballroom, Holiday Inn Gaithersburg, Two Montgomery Village Avenue, Gaithersburg, Maryland, Dr. L. Barth Reller, Chairman, presiding.

PRESENT:

L. BARTH RELLER, M.E., Chairman

GORDON L. ARCHER, M.D., Member

RICHARD E. BESSER, M.D., Member

JOAN P. CHESNEY, M.D., Member

CELIA CHRISTIE-SAMUELS, M.D., M.P.H., F.A.A.P., Member

ALAN S. CROSS, M.D., Consultant (voting)

PRESENT (Continued):

ROBERT L. DANNER, M.D., Consultant (voting)

STEVEN EBERT, Pharm.D., Consultant (voting)

G. SCOTT GIEBINK, M.D., Consultant (voting)

CHRISTOPHER HARRISON, M.D., Guest

JAMES E. LEGGETT, JR., M.D., Member

BARBARA E. MURRAY, M.D., Member

JUDITH R. O'FALLON, Ph.D., Member

JULIO A. RAMIREZ, M.D., Consultant (voting)

KEITH A. RODVOLD, Pharm.D., Consultant (voting)

DAVID E. SOPER, M.D., Member

JOSE A. VAZQUEZ, M.D.., Guest

ELLEN R. WALD, M.D., Member

C-O-N-T-E-N-T-S

P-R-O-C-E-E-D-I-N-G-S

(8:08 a.m.)

CHAIRMAN RELLER: Good morning. I'd like to welcome you to the Anti-infective Advisory Committee meeting to consider a new drug application, NDA 50-755 for Augmentin ES, amoxicillin/clavulanate from GlaxoSmithKline.

We'll begin the meeting with an opening statement from Tom Perez, our Executive Secretary.

Tom.

MR. PEREZ: Good morning. The following announcement addresses the issue of conflict of interest with regard to this meeting, and it's made part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interests in terms regulated by the Center for Drug Evaluation and Research which have been reported by the participants present no potential for an appearance of a conflict of interest at this meeting with the following exception.

In accordance with 18 USC 208(b)(3), a full waiver has been granted to Dr. Julio Ramirez. A

copy of this waiver statement may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

We would like to disclose for the record that Dr. Ellen Wald's employer, the University of Pittsburgh, participated in a study of Augmentin ES for use in the treatment of acute otitis media caused by penicillin resistant Streptococcus pneumoniae. Dr. Wald was named as co-investigator in the study. However, she had nothing to do with the study from its inception. She did not screen any patients, enroll any patients, review any data from the study, and has no knowledge of the findings.

Although this interest does not constitute a financial interest within the meaning of 18 USC 208(a), it could, however, create the appearance of a conflict of interest. The agency has determined notwithstanding this interest that the interest of the government and Dr. Wald's participation outweighs the concern that the integrity of the agency's programs may be questioned.

Therefore, Dr. Wald may participate in the discussions and deliberations of the committee without voting privileges in today's meeting regarding

Augmentin ES.

With respect to FDA's invited guest speakers, Dr. Christopher J. Harrison has reported interest which we believe should be made public to allow the participants to objectively evaluate the comments, his comments.

Dr. Harrison would like to disclose that he is on a speaker's bureau for SmithKline Beecham, has received consultant fees from SmithKline Beecham, and has participated in several studies funded by SmithKline Beecham, including one as co-investigator involving amoxicillin clavulanate.

In the event that the discussions involve any other products or first not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment up.

Thank you.

CHAIRMAN RELLER: I'd next like to introduce the members of the panel, and then we'll

have Dr. Dianne Murphy, the Director of OED IV, have her welcome and introduction.

Dr. Murphy was at the far right and is coming toward the podium.

Dr. Soreth.

DR. SORETH: Good morning. My name is Janice Soreth, and I'm the Acting Division Director for the Anti-Infectives Division.

DR. MAKHENE: Good morning. My name is Dikoe Makhene. I'm with the Division of Anti-Infective Drug Products.

DR. HE SUN: Good morning. My name, He Sun, Bio-Pharm. reviewer.

DR. ARCHER: I'm Gordon Archer. I'm Chair of the Division of Infectious Disease at the Medical College of Virginia, Virginia Commonwealth University.

DR. CHESNEY: Joan Chesney from the University of Tennessee in Memphis, the Division of Pediatric Infectious Disease.

DR. CHRISTIE: Celia Christie, professor and chair in pediatrics, University Hospital of the West Indies, and I also practice infectious diseases.

DR. CROSS: Alan Cross, Division of Infectious Diseases, University of Maryland in Baltimore.

DR. LEGGETT: Jim Leggett, Infectious Diseases at Providence Portland Medical Center in the Oregon Health Sciences University.

DR. MURRAY: Barbara Murray, Director of Infectious Diseases University of Texas Medical School in Houston.

DR. RAMIREZ: Julio Ramirez, Chief, Infectious Diseases, University of Louisville, Kentucky.

DR. SOPER: David Soper, Medical University of South Carolina in Charleston.

CHAIRMAN RELLER: Barth Reller, Division of Infectious Diseases and Director of Clinical Microbiology, Duke University Medical Center.

MR. PEREZ: Tom Perez, Executive Secretary for the Anti-Infective Drugs Advisory Committee.

DR. O'FALLON: Judith O'Fallon, biostatistician at the Mayo Clinic Cancer Center.

DR. WALD: Ellen Wald, Chief of Allergy Immunology and Infectious Diseases at the Children's Hospital, Pittsburgh.

DR. EBERT: Steve Ebert, infectious diseases pharmacist in University of Wisconsin and Meriter Hospital in Madison.

DR. GIEBINK: Scott Giebink, Director of

Pediatric Infectious Disease and Director of the Otitis Media Research Center at the University of Minnesota School of Medicine.

DR. RODVOLD: Keith Rodvold, Professor of Pharmacy Practice, Colleges of Pharmacy and Medicine, University of Illinois at Chicago.

DR. DANNER: Bob Danner, Critical Care Medicine Department, National Institutes of Health.

DR. BESSER: Rich Besser Respiratory Diseases Branch in the National Center for Infectious Diseases at the Centers for Disease Control and Prevention.

DR. HARRISON: I'm Chris Harrison, Professor of Pediatrics and Pediatric Infectious Diseases at the University of Louisville.

DR. VAZQUEZ: Jose Vazquez, Division of Infectious Diseases, Wayne State University in Detroit, Michigan.

CHAIRMAN RELLER: Thank you.

Dr. Murphy.

DR. MURPHY: I would like to thank everyone who's here this morning because we do have important clinical trial issues to discuss that are relevant not only to this application, but to future applications targeting penicillin resistant Strep.

pneumococci.

But before we delve into the data, which is what we all love to do, I'd like to take a minute and thank and recognize two members of our Advisory Committee who will be leaving the committee as formal members after this meeting.

I wanted to comment for those of you who have never been on an Advisory Committee meeting that it requires a tremendous amount of work and commitment, and it is a way to serve the public health. We are never able to really reimburse the individuals involved for the time and commitment they must put into this.

Having been on an Advisory Committee, I can tell you that you receive inches and sometimes a foot or so of data, and you can't just read it on the plane. You really do need to read the material, think about it, and come prepared to listen to the various persuasions that will be presented.

This requires a fair amount of effort, and we would like to recognize this morning our two departing members.

Dr. Danner, would you please come forth?

This is a certificate of appreciation to Robert Danner in recognition of distinguished service

to the Anti-Infective Drugs Advisory Committee, and we sincerely thank you for doing this for us.

DR. DANNER: Thank you very much.

(Applause.)

DR. MURPHY: Dr. Rodvold.

Dr. Keith Rodvold, who is our consumer representative, again, this is a certificate of appreciation in recognition of distinguished service, and we sincerely appreciate your efforts.

Thank you.

(Applause.)

DR. MURPHY: We have three new members, one who is not yet complete -- well, they have -- I guess we can say the FDA has not complete all of the paper work. So they are here today as a consultant, and that is Dr. Alan Cross, Dr. Julio Ramirez, and Dr. Steve Ebert.

So we look forward to their future participation with the committee.

Now, it is my task this morning to paint the broad picture and to emphasize for the committee the clinical trial design issues that have arisen during the review of this product.

Next slide, please.

We have had a number of sponsors bring or

come to the FDA and say, "We want to develop this product to treat resistant organisms." The epidemiology would say that the resistant organisms are out there. They have developed trials and have brought the data in, and we don't have the number of patients who have actually had the resistant organism, and the numbers have been a number of times now not sufficient to provide us with enough data to inform us how to really prescribe this drug and determine whether it is safe and effective for that population.

Therefore, this sponsor has done what this committee and a number of committees have advised one to do if you are going to develop trials to look at target resistant organisms, and Dr. Soreth will review for you this morning almost three decades now of efforts addressing the clinical trial approaches to otitis media and trials to target resistant organisms.

What we have is the modification of the trials in the form of population selection, and the recommendation from the committee that we have tympanocentesis at baseline and on therapy to determine the microbiologic response of the patient to the therapy.

Next slide, please.

You will hear us speak today about the

difference between all comers versus enriched populations. To put it in perspective, most trials, otitis media trials have had all comers, and actually the clinical trial for this application was, quote, an all comers' trial also. And you will hear more about the difference in these populations.

Next slide, please.

But to quickly summarize for you, if you're going to select a population that is going to be colonized and have organisms that are resistant, you have selected enriching your trial with patients who are younger and, importantly, you will note that this population has been selected for recurrence. It means that they have had previous episodes of otitis media versus excluded and other otitis media trials. There actually has been an active process by inclusion criteria or an analysis to exclude children who have had recurrence. So you will note that that is one important criteria for the population involved in the microbiologic study you will be hearing about today.

And it, therefore, can be presumed that these children have more antibiotic prior exposure.

Next slide, please.

When one enriches the population, one then has a population that is higher risk for recurrence,

and what we see in the data is a disconnect at times between the microbiologic response and the clinical response and what difficulty in the confounding that is occurring here: is it the population or is the drug?

That is what you're going to need to consider when you look at the data today because we will note that discrepancy between the microbiologic and clinical outcomes.

Timing is another issue that you will be asked to address because of the potential effect of the population on this.

Next slide, please.

And just as we don't have enough confounders in all of this, think about when you do tympanocentesis, when you do it the way you've been asked to do it, does this discrepancy received between microbiologic and clinical have anything to do with the fact that when you do the tympanocentesis on therapy, you would expect possibly to have suppression, maybe some antibiotic. You're not able to grow it. Is that what's going on, or is there the converse has happened where we have situations where we grow something at the second tap, and yet clinically the patient resolves? Is the

tympanocentesis actually an intervention?

Next slide, please.

So the question you're really going to have to struggle with is: does the lower rate of clinical cure in this type of trial, and we're talking about the microbiologic trial, reflect the characteristics of the population, the trial design, or the failure of the therapy to eradicate the resistant organism?

And we'll look forward to your discussion.

Thank you.

Dr. Sorest, I believe, will now provide a refresher for you of where we've been and how we got here.

DR. SORETH: Good morning. The following represents about a quarter century worth of guidance that we have developed within the Division of Anti-Infectives, but I promise I'll be speaking for less than ten minutes.

Next slide, please.

In 1977, we wrote the guidelines for the clinical evaluation of anti-infective drugs with regard to acute otitis media. This document has perhaps two or three paragraphs with regard to studying a drug for otitis, and the number of trials

is not really specifically addressed, although I think at the time, then as now, the interpretation of adequate and well controlled studies was that you would need two.

The case definition is given in general terms that a child should have clinical evidence of acute otitis media with inflammation of the tympanic membrane and middle ear, again, not further defined in that guidance.

Tympanocentesis was noted to be required in studies at baseline for all patients, and a second tap, this guideline goes on to say, is desirable to obtain data on middle ear fluid concentrations of the drug, as well as promptness of bacteriologic cure.

Regarding endpoints, the guidelines stressed then both clinical and microbiologic endpoints, and although it's not specific with regard to test of cure, it mentions that patients should be followed for at least four weeks after their last dose of drug.

Let's switch gears now to the '90s and talk about -- oh, I'm sorry. One other point from the '77 guideline was the following: that in the absence of culture of the middle ear fluid, no specific claim could be made regarding the effectiveness of anti-

infective drugs.

So both trials at that time stressed the importance of the underpinning and proof of microbiologic etiology of the infection.

In 1992, the division authored the points to consider document, and on the point of number of clinical trials, it states that two are suggested.

However, now comes a change in the paradigm, and one of those two studies could be a clinical only study, that is, no tympanocentesis or tap would be required at baseline. This would be a comparative study with another drug to establish equivalence to that already approved product for acute otitis media.

The second study then should be a clinical microbiologic study. It could be uncontrolled, and it would have tympanocentesis at baseline.

Next slide.

The case definition this guidance in '92 stated should be rigid, although it wasn't specific in what that rigid case definition should be.

Tympanocentesis was strongly encouraged in all those patients judged to be therapeutic failures whenever they were judged to be failures. Endpoints were both clinical and microbiologic, and I would say

each were given equal weight.

And with regard to test of cure, it's not specifically addressed. Again, what was different about this guidance is on the next slide, for we became very specific in terms of what we wanted to see in that open micro trial.

It should establish acceptable microbial and clinical outcome in at least 25 patients with Haemophilus influenzae, 25 patients with Streptococcus pneumoniae, and in at least 15 patients with Moraxella catarrhalis.

Also in '92, the IDSA FDA guidelines were published on studying acute otitis media, and these very much are in sync with the points to consider document. Two trials are suggested, a bit larger study I would say for the micro study, and a comparative clinical trial where a tap would be optional, but where a double blind paradigm was strongly encouraged.

The case definition listed clinical criteria, although, again, it doesn't read like a protocol in terms of you must have three or four in order to be considered eligible for enrollment in the trial.

Tympanocentesis, again, was required in

patients or heavily emphasized in patients who were not clinical successes, and with regard to endpoints, clinical and microbiologic were stressed.

And finally, test of cure was recommended to be one to two weeks after completion of therapy.

Next slide.

At the end of the decade of the '90s, the division made another attempt to get very specific about what it was looking for in working with sponsors, developing drugs for acute otitis media, and we brought an evaluability criteria document on otitis before two advisory committees, both in 1997 and 1998.

Two trials were suggested, again, a micro study, noncomparative, but the Advisory Committee at those times recommended that we increase the number of patients in that trial so that we would have more of an experience with the three major pathogens that underpin this diagnosis, as well as perhaps gain some experience with resistant organisms, and a second comparative clinical trial.

The case definition you recommended to us should be tightened a lot so that children would be enrolled in the trial if they had bulging tympanic membranes, if there was documentation of impairment, of the mobility of that tympanic membrane with

biphasic pneumatic otoscopy, et cetera, trying to get away from trials which enrolled an irritable child with a red TM, which we know in a clinical only trial will allow for a number of patients who don't have a bacteriologic etiology for their infection.

With regard to tympanocentesis, the committee heavily stressed in those years that we consider asking sponsors to repeat the tap at study day three to five or four to six as a critical measure of the effectiveness of the drug, and again, to perform tympanocentesis in all failures.

Endpoints that were stressed were, again, clinical cure at the test of cure, defined as a few weeks after the last dose of drug, as well as pathogen eradication.

I don't think there was as much discussion during these committee presentations in '97 and '98 as we would have liked, at least on the point of pathogen eradication, and when was really the most relevant or most important timing for assessment of that outcome measure, though in our guidance document we state the following then as now.

Next slide.

With regard to the microbiologic endpoint tympanocentesis obtained at the on therapy visit

should not be considered evidence of documented eradication. Rather, a negative culture result may represent antimicrobial suppression.

Also in '98 the committee encouraged us, and we took to heart the statement that we should encourage sponsors to enroll more patients under the age of two and to gain much more experience with drug resistant Streptococcus pneumoniae.

Next slide.

And so we've come to this point where in order to enrich for children with drug resistant Streptococcus pneumoniae, we have changed essentially the inclusion/exclusion criteria for our traditional all comers trial.

To increase the number of patients under two months of age has implications for we know from experience and literature that children under two typically have higher rates of failure or relapse.

In an enriched trial, one would enroll patients with recently ruptured tympanic membranes, as well as a history of recurrent otitis, three infections in six months, four infections in 12 months, as well as children currently on antibiotic prophylaxis.

In an all comers trial, some of these

features are typically exclusion criteria.

Furthermore, to include patients who had recent episodes of acute otitis who failed courses of antibiotics, again, enriching for experience with DRSP. I think that these enrichment strategies that I've enumerated here to gain experience in children with DRSP in otitis raise fundamental questions regarding clinical trial design, and Dr. Murphy has already pointed to some of these.

Namely, those issues are the importance and the relevance of outcome measures, clinical outcomes as well as microbiologic outcomes, and the importance of the timing of those assessments, whether it's a microbiologic outcome measured on therapy, day three to five or so into the study, versus a tympanocentesis that's performed off therapy at the time of, say, clinical failure or relapse.

With regard to clinical outcome, the importance of looking at data at the end of therapy recently, a child recently finishing their last dose of drug versus several weeks out.

I think that the discussion of these important clinical trial design issues, the measurement of endpoints and the timing of those measurements, together with what we will learn about

the natural history of otitis and what we know about -- the little that we know about placebo controlled trials will then allow for a fuller discussion of the specific data that GlaxoSmithKline and the FDA will present to you today and allow for an interpretation of those data.

I'll stop here and turn the podium over to Dr. Scott Giebink, who will be talking about the natural history of acute otitis media and epidemiology with specific emphasis on drug resistant Strep. pneumoniae.

Dr. Giebink.

DR. GIEBINK: Thank you, Dr. Soreth.

I thank the panel for inviting me back again to continue with the discussion of otitis media. If I'd had enough room on this slide, the true title would be otitis epidemiology and DRSP as related to enhancement and test of cure because those are two issues that I'd like to round out a bit more as we talk.

Next slide, please.

Well, as this group well knows, there are millions of cases of acute otitis media a year. Using rather loose case definitions largely coming from claims based data, probably about 24 million per year.

About 80 percent of children have at least one episode by the time of their third birthday, and many researchers believe that this actually may be closer to 100 percent.

About half of children have more than three episodes by their third birthday, and we know that largely otitis media recurrence has defined itself by the second birthday. Those children who develop recurrent otitis media have had an episode by that second birthday.

And we also know that between seven and 12 million cases a year are caused by Streptococcus pneumoniae, hence the focus on pneumococcus.

The next slide.

In those studies, one by Dr. Mandell in Pittsburgh, and one by Dr. Del Beccaro in Washington that used very fastidious microbiologic techniques, where broth cultures were employed.

You'll notice that the wedge of pie here containing the pneumococcus is at 50 percent in these two studies. You'll also notice that only six percent of these air cultures yielded no bacteria on culture. I think that's an important fact because if you look across the literature at all studies taken together, you'll see numbers in the 30 to 40 percent range for

pneumococcus.

And largely when fastidious techniques are used, it's the pneumococci that come out, not Haemophilus and not Moraxella. So that the impact of pneumococcus, I believe, is greater than is reflected by many studies, and I believe this is a more accurate representation of bacterial etiology of AOM.

Next slide.

Now, to the issue of enhancement, these data, I think, are revealing. This comes from the study by Dr. Phil Kaleida in Pittsburgh in the late 1980s, so that we're not seeing hardly any resistant pneumococci, but you'll notice that when mild and severe disease was separated, and I'm reminded of Dr. Murphy's comment, the children in the trials we're talking about today had to have red, bulging eardrums. This would be categorized by most as severe acute otitis.

And here's the enrichment that you see. Twenty percent of mild disease caused by pneumococcus, 38 percent of severe disease caused by pneumococcus, and the opposite with Haemophilus influenzae.

Now, this difference didn't reach significance, but there's almost a twofold difference there for pneumococcus alone.

These respiratory bacteria are not the only cause of otitis media. We know particularly from studies in Galveston, Texas and in Finland where very sophisticated techniques have been used to look for respiratory viruses that somewhere between 50 and 70 percent of AOM disease is accompanied by a respiratory viral infection.

Now, you'll notice on the far left in this Finnish trial that about two thirds of the pneumococcal otitis occurred in the absence of a respiratory viral infection, only about a third with a respiratory viral infection, in contrast to Haemophilus, Moraxella, and the absence of a bacteria where about a half to two thirds were accompanied by a respiratory virus infection.

And we know that RSV influenza, pair influenza (phonetic) are the leading respiratory viruses accompanying otitis.

Next slide.

Now the pathogenesis of otitis media, and I think this is a remarkable feat. Never have I put pathogenesis into one slide with a cartoon, but this is really the crux of the matter, that respiratory viral infection is probably the single biggest factor that leads to eustachian tube dysfunction and actually

a physical obstruction with mucus and cellular debris.

There are some children who have anatomic abnormalities that cause tubal dysfunction, but for the vast majority of children, it's respiratory viruses, and we'll come back to this point when we talk about the out-of-home child care impact on otitis.

With an obstructed eustachian tube, middle ear -- nasopharyngeal bacteria invade the middle ear, and as organisms replicate, there is an influx of inflammatory cells produced by the release, the very early release of inflammatory mediators, such as the pro inflammatory cytokines.

We can't lose sight of the fact that otitis media is an inflammatory process in the middle ear, and simply eradicating the bacteria from that milieu does not necessarily turn off the inflammatory process, and that inflammatory process, as has been shown in several studies, is associated with continuing clinical signs and symptoms.

Next slide.

Otitis media is a disease continuum. It begins with the subject we're talking about today, acute otitis media, which uncommonly these days is associated with suppurative complications like the

chronic suppurative otitis through a chronic perforation, mastoiditis, meningitis, and facial nerve palsy.

Although most clinicians would tell you that the rates of acute mastoiditis or subacute disease have increased in the last decade, there are not epidemiologic data broadly in the population to substantiate this, but it's a clinical impression.

Many cases of AOM go on to chronic otitis media where the fusion in that inflammatory process continues, and there's a remarkable transition in the middle ear epithelial cells in these cases of AOM where the epithelial cells undergo metaplasia and become secretory cells secreting a mucus glycoprotein that has now been identified as to the mucin genes responsible for this mucus glycoprotein. That's the entity that leads to tympanostomy tubes, which is the largest surgical procedure performed on children in the United States.

Some cases of chronic OME in the long-term studies, probably five to ten percent of children who end up with tubes will go on to these non-suppurative complications. We hear a lot of talk about hearing loss and the resulting school performance issues, but there are significant tissue pathologies as well, such

as atelectasis, adhesive otitis, cholesteatoma, and damage to the middle ear ossicles that can result non-suppuratively from this chronic inflammation.

That is the disease continuum. When we say the two words "otitis media," we mean this whole thing.

Next slide.

And, of course, pneumococcus in causing otitis media, certainly the base of the pneumococcal pyramid is the mildest of the pneumococcal diseases, and we have upwards of half a million cases of pneumonia in children a year, probably about 50,000 cases of bacteremia, and about 3,000 cases of meningitis.

So pneumococcal disease among children and adults, especially elderly adults, is a major health problem.

Next slide.

And all of this begins because pneumococci colonize the nasopharynx, and they successfully evade mucosal defenses and cross that barrier either directly into the blood stream where they can lead to sepsis and meningitis or they invade locally, such as in the case of otitis media and sinusitis, where they evade the local mucosal defenses and either move up

the eustachian tube or into the sinus ostium causing inflammation there.

And in some cases if a certain threshold of organisms on that mucosal surface is exceeded, the organisms can invade at a later date and cause bacteremic disease, and this is probably the mechanism for bacteremic pneumonia.

Slide.

Carriage rates are extremely high in preschool children, and as you know, much higher in children who attend out of home child care than in children cared for at home. These rates decrease from about 60 percent to about 35 percent in grammar school, down to about 25 percent in high school, and to a low of about six percent in adults who do not work in a day care center, and who don't have preschool children at home, but if they do, then those adults are very likely to be carriers of pneumococci.

Next slide.

And of course, antimicrobial resistance among these three major pathogens causing AOM has become a major problem in the last two and a half decades. Initially heralded by the increase in Moraxella resistance, then the increase in Haemophilus influenzae resistance, both largely mediated by beta-

lactamase, and really an all or none process of resistance, one that cannot be overcome simply by increasing concentrations of antibiotics, certainly not beta-lactamase abalics (phonetic).

In contrast, pneumococci, which have become a major problem with resistance in this last decade, are resisted by virtue of their altered cell wall and altered penicillin binding proteins, and that is a process that can be overcome by increasing concentrations of beta-lactam drugs.

Next slide.

So just by way of overview before I dive into some numbers, the major pneumococcal resistant trends have tended to be very strongly associated with a very few of the 90 pneumococcal serotypes that have been identified, and the great majority of these are included in the recently licensed 7-valent pneumococcal conjugate vaccines.

We know that susceptible strains can acquire resistance over time, and there have been cases reported from child care centers where this has been observed in individual clones.

These resistant strains are becoming more resistant to other classes of antibiotics, and I'll show you those data in a moment.

Over the past two-plus decades you can see the rates of rise of these nonsusceptible pneumococci, the first one actually isolated in the United States in 1975, and now upwards of 24, 25 percent showing nonsusceptibility.

Now, there is an issue where the change in NCCLS breakpoint for amoxicillin that's not indicated here, and I'll mention that in just a moment.

So there has been quite a rise during the '90s and a leveling off in the last couple of years.

And by the Thornsberry article, which represented about 2,700 isolates at 51 medical centers in the United States, collected between '96 and '97. You'll notice that the lowest areas of susceptibility -- I don't know if you can see -- the lowest areas of susceptibility down here in South Central, and generally the rest of the country, about 65 to 70 percent of pneumococci show susceptibility to penicillin.

Slide.

Now, these are the data, and I just want to call your attention to some groups of data here, not all of these numbers, and we'll focus just on the far right-hand column.

In this study and at that point the NCCLS

breakpoint for amoxicillin was one microgram per mL, and you'll notice here that about ten percent of penicillin resistance pneumococci were susceptible using that breakpoint to amoxicillin. Point eight percent to amoxicillin-clavulanate, and this difference is an issue that might deserve some comment later on.

The cephalosporins are interesting because there is a difference among the cephalosporin. Here, a second generation and two third generation cephalosporins.

In the percent of these pen-resistant strains susceptible to these two groups of cephalosporins about 30 percent of macrolides, about 30 percent of pen-resistant strains that are sensitive to macrolides.

Slide.

The quinalones remain quite active against pneumococcus, at least in '96-'97, with the vast majority of the pen-resistant strains susceptible to these quinalones. Most of susceptible to clindamycin, rifampin, and all are susceptible to vancomycin, tetracycline, and trimethoprim-sulfa, considerably less activity against the pen-resistant strains.

Slide.

Now, there are two interesting factors, again speaking to the issue of enrichment, that emerged from this study. You'll notice here that among the 85 ear isolates from this group of pneumococcal isolates, all of these antibiotic activities are less for the ear isolates than they are for the blood and CSF isolates.

And just take penicillin for an example. Forty-four, 45 percent of the ear isolates susceptible to penicillin, 78 percent of the invasive blood and CSF isolates susceptible, and that's true all the way down the line.

So when we enhance for ear disease and enhance for pneumococcal ear disease, we end up with more resistant strains.

Slide.

And age is another enhancing factor. The younger the child, the more likely those strains are to be antimicrobially resistant. Here you'll notice that with penicillin 49 percent of these 284 strains were resistant -- were susceptible versus 70 percent in the older group of children and adolescents and young adults.

A study that just appeared in the New England Journal a week or two ago by Whitney shows the

change in susceptibility to these antimicrobials over the four years, '95 to '98, and you can peruse this at your leisure.

I want to call your attention to this group of bars on the far right of the slide. You'll notice that the proportion of isolates resistant to more than two drugs -- so this is three or more drug classes -- has increased from about nine percent to about 14 percent over those four years.

So multi-drug resistant Strep. pneumoniae is an increasing problem.

Next slide.

Now, I mentioned early in the discussion that the vast majority of these resistant pneumococcal types are contained within the serotypes covered by the recently licensed conjugate vaccine.

However, if you look at the right side of the slide, these are data from the recent article by Whitney in New England Journal; that there are other types. In fact, 21 percent of types not mentioned on this slide showed resistance to penicillin.

So penicillin resistance is spreading beyond those types covered by the conjugate vaccine, the 7-valent vaccine.

Slide.

The issue of child care I've alluded to before. This is a study by Dr. Wald about a decade ago showing the remarkable increase in rates of otitis media complicating URIs among children cared for at home in the first year of life, this set of bars on the left; those cared for in a small group, and those cared for in the center.

And difference, although it lost significance in the following two years, the trend was largely the same. And group child care or center child care, of course, enhances for respiratory viral exposure and the transmission of these resistant pneumococci.

Slide.

An interesting study appeared in Clinical Infectious Disease last year looking at the spread of a multi-drug resistant Type 14 pneumococcus in a Tennessee community with three different day care centers, and when surveillance studies were done in this community and compared with the pediatric practice, you'll notice not only was this Type 14 clone present in 20 percent of the children in the day care that had the three cases of meningitis. It was also present in two other day care centers at rates of about ten percent, not in the general community, and

was buried within a sea of other pneumococcal serotypes.

Slide.

Now, I show you this more as a scatter plot than for the numbers. These are data from eight different day care centers in Beer-Sheva, Israel that Dr. Rhonda Gann's group collected during a very short period of time between October '96 and February '97, also published in Clin. Infectious Disease last year.

And shown here are seven different clones either by virtue of a difference in serotypes or resistance patterns, and you'll notice that during this very short period of time, these clones were spread throughout the community, throughout these day care centers in different patterns.

So to say that an antimicrobial resistance clone is spreading through a community and only say that ignores the impact of pneumococci in the child care population out of home.

And it's interesting to look at -- these numbers, incidentally, are percent of children carrying that particular strain.

Slide.

The group looked at whether chemoprophylaxis with seven days of rifampin and

clindamycin had an effect on carriage in the first day care center that had the three cases of meningitis. You'll notice that there was a very dramatic reduction in carriage immediately after completing prophylaxis that that rapidly rebounded to baseline levels.

So chemoprophylaxis has not been effective over the long term.

It was interesting in this study that none of the strains isolated here three and a half months later were rifampin or clindamycin resistant strains.

Slide.

And finally, just a couple of comments on markers of antibiotic effectiveness. As this group certainly knows better than I, bacteriologic efficacy with sterilization of middle ear fluid is one. It's been thought of as the gold standard, if you will.

Clinical efficacy is the resolution of clinical signs and symptoms, and in the studies that are being discussed today, this is the test of cure at about one month, and pharmacokinetic surrogates that the group has discussed extensively in the past in the understanding that time over MIC is a very important pharmacokinetic surrogate of pharmacodynamic activity.

Slide.

One of the issues with otitis media

pneumococcal and -- I apologize for the way this slide is coming out. This is the study by Phil Kaleida a decade ago in Pittsburgh showing the spontaneous resolution rate in mild and severe acute otitis media.

If you do the math on this number with severe otitis media and recognize that it's quite unlikely that pneumococcal otitis will spontaneously resolve and much more likely that Haemophilus and Moraxella disease will, you would get a number very close to this just through the armchair mathematics.

And of course, amoxicillin -- this amoxicillin should be over here -- only is causing a significant rate difference, but a relatively small difference for mild disease.

Slide.

And here is, I think, perhaps one of the most important articles in the otitis literature related to bacteriologic versus clinical outcome. It's a compilation of studies that Dr. Colin Marchant, Dr. Johnson, Carlin, and others in Cleveland put together during the 1980s, where taps were done on treatment and looked at the relationship between clinical and bacteriologic outcome.

The sensitivity of the clinical outcome right here is extremely high so that among the 253

bacteriologic successes, 236, 93 percent of them, were clinical successes.

The problem is with specificity, and in this compilation of studies, among the 40 bacteriologic failures, 25 of them were called clinical successes. Only 15 were called clinical failures for a specificity of 37 percent.

Slide.

And thus we have fallen as the panel here as recommended on the so-called two tap studies, where ears are tapped on treatment, and these studies -- and I've just assembled some data that Dr. Dagan shared with me a couple of years ago, and this has been updated since then.

You'll notice as you move across from sensitive to intermediate to resistant strains that there is a decreasing bacteriologic response rate. The failure percentage increases, and you'll also notice that there is quite a difference in bacteriologic response rate among these different antibiotics that is not revealed by the clinical response rates.

Slide.

And Dr. Marchant wrote an article nine years ago describing this phenomenon that he termed

situation to exist.

One is the reinfection of the middle ear either with a susceptible or a resistant organism

The second is that the concurrent viral infection, which we've already seen is a major cause of, antecedent of the bacterial infection, is still causing clinical signs and symptoms.

And the third is that, in fact, the drug has been successful, has eradicated the organism. It's bacteriologically active, but the persistent middle ear inflammation and the presence of those mediators in the middle ear continues to recruit white cells and continues to cause erythema and pain.

And I think those are the three factors that need more discussion as an underlying cause of bacteriologic success and clinical failure.

Thank you.

CHAIRMAN RELLER: Thank you, Dr. Giebink, for that scholarly review that I think will prove very helpful for the subsequent discussions.

We now turn to the GlaxoSmithKline presentation,a nd the background and overview will be presented by Dr. David Cocchetto.

DR. COCCHETTO: Thank you, Dr. Reller.

Good morning. Mr. Chairman, Dr. Soreth,

members of the Advisory Committee, consultants, and guests, my name is David Cocchetto, and I'm a member of the team at GlaxoSmithKline working on Augmentin ES.

On behalf of our company, we appreciate the opportunity to talk with you today about Augmentin ES.

Next slide.

Now, Augmentin ES is a powder for oral suspension. It contains a 14 to one ratio of amoxicillin to clavulanate, which as you know is twice the ratio in the currently marketed product.

The Augmentin ES formulation enables us to provide 600 milligrams of amoxicillin per five milliliters of constituted suspension, and that, in turn, facilitates delivery of the dosage of 90 milligrams per kilo per day of the amoxicillin component, which is twice the dosage that's currently approved for Augmentin.

Next slide.

Now, Augmentin ES was developed in response to two particular needs. First of all, as Dr. Giebink has already described, the increasing public health concern about the prevalence of penicillin resistant Streptococcus pneumoniae in the

population.

Secondly, over time, we became increasingly aware of reports of concomitant prescribing of Augmentin plus supplemental amoxicillin for the treatment of selected cases of acute otitis media.

Next slide.

Dr. Soreth has already summarized previous guidance in this area. I would only say that FDA, this Advisory Committee, and the IDSA have all been important participants in the process of providing guidance. It's been quite informative.

Most recently we've already talked about the July '98 meeting of this committee, where as it's been reviewed, repeat tympanocentesis was viewed as an important feature of study design for assessing efficacy specifically against PRSP.

Now, the history of this particular NDA for Augmentin ES subsequent to the public Advisory Committee discussion in July of '98, we provided to develop a protocol which you'll come to know as clinical study 536, specifically to assess acute otitis media due to penicillin resistant pneumococci.

That protocol was submitted to FDA, and its design was discussed prior to initiating the study

in 1999, and that study, as you know, uses repeat tympanocentesis to assess the primary endpoint of bacterial eradication on therapy.

Next slide.

Now, the results of that study are one of the two sets of results of clinical studies of acute otitis media included in the new drug application.

In addition to study 536, we also supplied results of a study conducted a couple of years earlier, study 447, which is a clinical study of safety and clinical outcomes comparing Augmentin ES with Augmentin in 553 children with acute otitis media.

Next slide.

Based on these studies, we've proposed the following indication: that Augmentin ES be indicated for the treatment of acute otitis media caused by beta-lactamase producing strains of Haemophilus influenzae or Moraxella catarrhalis and Streptococcus pneumoniae, including penicillin resistant strains which are defined as strains having an MIC value for penicillin greater than or equal to two micrograms per mL when such strains are suspected.

Next slide.

For the remainder of the sponsor's time on

the agenda, we have a series of speakers that will address topics in acute otitis media, starting with Dr. william Craig, who is the Chief of infectious Disease at the Middleton Memorial Veterans Hospital and Professor of Medicine at the University of Wisconsin.

Dr. Craig.

DR. CRAIG: Committee members and interested guests, my task is to review with you the importance of time above MIC for the in vivo activity of Augmentin and other beta-lactams in acute otitis media.

The pharmacology of antimicrobials can be divided into two parts. Pharmacokinetics is concerned with the absorption, the distribution, the elimination of drugs, and it's those factors combined with the dosage regimen that determine the time course of concentrations in serum, which in turn determine the time course of concentrations in tissues and body fluids, and of course, at the site of infection.

Pharmacodynamics, on the other hand, is concerned with the relationship between concentration and the pharmacologic and toxicologic effect, and again, with antimicrobials, what we're interested in is the time course of antimicrobial activity.

Now, the primary parameters for measuring antimicrobial activity over the years have been the minimal inhibitory concentration and the minimum bacteriocidal concentration. While these are good indicators of the potency of a drug against an organism, they tell you absolutely nothing about the time course of antimicrobial activity.

The parameters that are much more important in describing the time course are the rate of killing and the effect of increasing concentrations on that killing rate and then persistent effects which go under a variety of names, such as the post antibiotic effect, the post antibiotic sub-MIC effect and the post antibiotic leukocyte enhancement.

Now, if we look at the pattern of antimicrobial activity with beta-lactam antibiotics, including amoxicillin, first of all, we find these drugs exhibit time dependent killing.

What I mean by that is that higher concentrations will not increase the rate of killing as compared to lower concentrations. So the only way to increase the extent of killing is to keep the drug around for a longer period of time. So the amount of killing is time dependent.

Furthermore, these drugs exhibit only

minimal to moderate persistent effects. In other words, the organism recovers relatively soon after concentrations fall below the MIC and start to grow again.

So the goal of a dosage regimens for these type of drugs would be to optimize the duration of exposure, and one would predict that time above MIC would be the major parameter correlating with efficacy.

Now, this can be proven in animal models. I show you this one. It's with a different organism, but with cefotaxime against Klebsiella pneumoniae in a pneumonia model in mice. This is published data, and what we're looking at here is the number of organisms remaining in the lung after 24 hours of therapy. About 40 different dosage regimens were used in these studies, and what we're looking at here is the relationship between those bacterial numbers and the peak to MIC ratio for those different dosage regimens.

The dotted line represents the starting point in terms of bacterial numbers. So points above this represent growth. Points below it represent killing.

And as you can see on this slide, it's

essentially quite -- shows really no relationship at all, essentially a scattergram.

Here, again, now we're looking at the relationship with the area under the curve, or the amount of organism to which the organism is exposed, although there tends to be a trend a better effect with a higher dose. Again, there's a huge amount of scatter for any one area under the curve.

However, when we look at time above MIC, we see all of the data collapses very nicely, clearly showing that time above MIC is the important parameter for this drug-organism combination.

Now, getting a little bit more specific for what we're addressing today, here is, again, a study looking at amoxicillin with Streptococcus pneumoniae in our murine thigh infection model, and there's two things that I want to point out specifically with this, is the so-called static dose. That's the dose that results in no net change over a 24-hour period, and so we're looking at the -- you'll see later I'll be referring to the time above MIC required for a static dose.

And then the other point that I wanted to point out is that the two log kill have from a variety of studies not only in our lab, but in other labs,

suggest that if you get two logs of kill within the first 24 or 48 hours, that can be translated into very high survival in the animals and complete eradication if one treats the animals out for longer periods of time.

Next slide.

Now, as I said, there have been a variety of studies done over the years looking at these pharmacodynamic parameters, and they have answered several important questions. The first question is: is the magnitude of the parameter required for efficacy the same in different animal species, including humans?

In other words, is the time above MIC that's required for efficacy in mice and rats the same time above MIC that's required for efficacy for treating human infections? And I hope I will show you data for which that answer is yes.

And that's a very nice thing if that is true because it allows one then to use animal models to start making predictions about what one would see especially in those situations where it's difficult to collect adequate clinical data.

And where do we always have that problem is with new emerging resistance.

Other questions that come up is does the magnitude of the parameter vary with the dosing interval, dosing regimen, and again, the studies have shown no, as long as you look at the time above MIC as a percent of the dosing interval.

Does it vary with different sites of infection? Again, from animal models, looking at blood, lung, peritoneum, and soft tissue, there appears to be no variation, and I'll show you some data to suggest that the sinus also behaves very much as the middle ear.

Does it vary with different drugs within the same class? Here we do see some differences. Penicillins require less time above MIC than with cephalosporins. We think this is related to the rate of killing of the drugs being faster with penicillins than with cephalosporins.

However, within any group, one does not see any difference providing one uses free, unbound drug for calculating out the time above MIC.

And fourthly, different organisms. Does it vary for different organisms, including resistant strains? Here the answer is yes for some, but at least with what we're dealing with today, there appears to be no difference for penicillin resistant

pneumococci, and that's illustrated on the next slide for two drugs, amoxicillin and cefpodoxime , which have very low protein binding in mice.

And what one is looking at here is the time above MIC for the static doses for a variety of different strains with varying MICs. Obviously organisms up at this end have the penicillin resistant strains while organisms down at this end are penicillin susceptible strains.

And as one can see, there appears to be no significant change, and if you drew a line through here, it would be horizontal, the same thing for amoxicillin and, again, also showing that at least for the penicillin here, it requires less time above MIC than the cephalosporin.

And so that if we look at time above MIC for the beta-lactams, we find that using as a percent of the dosing interval that the amount that is required for a static dose against most organisms in neutropenic mice varies from about 25 to 35 percent for penicillins, and from about 30 to 45 percent for cephalosporins.

Now, not all bacteria will grow in neutropenic -- in normal animals, and so that's why most of the time neutropenic animals are done. That's

specially true for penicillin resistant pneumococci.

However, if one looks at susceptible strains, which you can get to grow in normal mice, one finds that the presence of neutrophils further reduces the time above MIC that's required for efficacy by about five to ten percent.

So that three drug levels of penicillins and cephalosporins needed to exceed the MIC, somewhere between 35 for 50 percent of the dosing interval to produce maximum survival in animal models, with the penicillins being at the lower end of this range, and with the cephalosporins being at the higher range.

Next slide.

Here, just to give you an example, is two studies, a pneumonia model where the animals were sacrificed after 48 hours of therapy, and then the thigh model where we're looking at 24 hours. And what we're looking at is the change in the number of organisms over that period of time.

And whether one's looking at the thigh or looking at the pneumonia, one gets essentially the same curve, and as one can see here, that as soon as one gets above 40 percent above the MIC, one has at least a two log kill for these various organisms.

If we also go to the literature and try

and find all of the data on Streptococcus pneumoniae in which survival was used as an outcome and to plot that data against time above MIC, this is what is obtained. About 85 percent of the data with penicillins reflects data with amoxicillin, and one can see that when one gets to about 35 to 40 percent, one gets very good survival with the penicillins. It appears that one requires a little bit higher amount with the cephalosporins in order to get that same high degree of survival.

Now, for the human model, I'd like to thank all of the pediatricians that over the years have done some of these double tap studies that allowed us to take the bacteriologic cure data for different beta-lactams against pneumococci and also against Haemophilus influenzae from double tap studies to actually then see if there was a relationship between time above MIC in serum and the bacteriologic cure in otitis media.

Fortunately, there have also been some double studies done in acute maxillary sinusitis, which I will also show you on the slide.

Now, our initial publication on this in 1996 was primarily limited to penicillin susceptible strains, but fortunately investigators such as Ron

Dagan have done a variety of studies since then that include got penicillin intermediate and penicillin resistant strains, and so we can look at those studies separately from the penicillin susceptible isolates.

And then, as I mentioned, Jack Gwaltney and Mike Scheld over the years have done some sinusitis studies in which double tap studies were performed. Again, the great majority of these are with penicillin susceptible strains.

Here is sort of a summary of all of those results, looking at the relationship between time above MIC and bacterial eradication. The data with otitis media is show by the circles. The data with maxillary sinusitis is shown with squares, and just to, again, support the FDA and their wisdom in the past for many of the susceptible strains of giving approval to numerous oral drugs, we can see that for pneumococci susceptible strains, the bacteriologic cure is up in the 85 to 100 percent range for almost all of the regimens. It's only when a few of the drugs were dosed less frequently than the approved dosages that one starts then to find some failures with susceptible strains.

On the other hand, if we look with the penicillin intermediate and the penicillin resistant

Strep. pneumo., here we clearly see failures, but I want to point out that if one does get the time above MIC up above 40 percent, even for those organisms, one can obtain very excellent bacteriologic cure in otitis media.

Haemophilus influenzae, as you can see, also seems to fit along very nicely with what one sees with the pneumococcus, and secondly, I'd also like to point out that if one looks at the squares in relationship to the triangles, that sinusitis appears to behave very similarly to what one sees with the data with otitis media.

So our general conclusions would be that time above MIC is the important determinant of activity for beta-lactams against major respiratory pathogens, including penicillin resistant pneumococci, and that studies in acute otitis media and sinusitis demonstrate a good correlation between the time above MIC required for bacteriologic cure of pneumococci and the time above MIC required for either a two log kill or 90 to 100 percent survival in various animal models.

Well, what does this theory predict for this new formulation of Augmentin? And we have a little bit of data to look at. I'll show you first an

animal study, a pneumonia study in rats where human pharmacokinetics were simulated, and where the new dosing regimen was compared with the older dosing regimen.

And then I'll also show you some pharmacokinetic data, some extrapolated data from five children that received the older dose, the lower dose, and then a recent study in 18 children that received the higher dose. These were children with a mean age of five and range in age from 0.3 to 11 years.

Now, the mean drug levels for both of these studies were provided in your prior documents. Here is what we see with the animal model. What you see here is the number of organisms in the lung at 72 hours. There's a bunch of points by zero. That resembles what one sees in the control animals, and then the points that are out here in terms of time above MIC are what one sees for various organisms with MICs from two, four, and eight.

Now, as we see here with the older dosage regimen, this is half of this given BID, what one finds, it is only with the organism with an MIC of two that one essentially gets a two log kill, and there are a variety of other studies also published in the literature showing that with this type of dosage

regimen, one gets very good kill of organisms with MICs of two, but when one sees MICs that are higher, one starts to clearly see failures.

However, if we look at the newer dosage regimen, twice as high, now we see even a better effect with the MIC of two. We see clearly a two log drop for the organisms with an MIC of four. However, for the organism with an MIC of eight, we see no change.

Again, again, if we look at what time above MIC we're talking here, it's roughly around 34, 35 percent.

Next slide.

If we look then at the extrapolated data, this is the real data in five children. This other curve in blue is extrapolated by doubling the dose.

What we find here at this lower level here of an MIC of two, we find that we're above the MIC for 41 percent of the dosing interval. This kind of information combined with the animal data showing good kill of organisms with MIC of two, plus other clinical data that was presented to the NCCLS, was the factors that helped the NCCLS change the breakpoint for amoxicillin, giving it a breakpoint, a susceptibility breakpoint of two.

For the organisms with an MIC of four, we find here that with this regimen, the old regimen, we're only above the MIC for 28 percent of the time, and so one would predict that we would start to see failures with those such strains.

On the other hand, extrapolating this to the higher dose, we find now that we would have time above MIC Of 41 percent for MICs of four, but again, when we get up to eight, one would again predict that we would see failures.

Looking at the last slide, which is, again, the data from the trial looking at the actual suspension, these are, again, the mean concentrations. Again, the calculations or the extrapolation appears to be virtually the same for the eight: 28 percent above MIC.

However, when we look at the four in the actual patients, it's a little longer than was seen with the extrapolation, 46 percent versus 41 percent, and similarly when we look at two, again a little higher, 57 percent versus 50 percent.

So, again, based on the predictions here and the time above MIC, we would predict that the clinical data would show very good results for organisms with MICs of four and two, and that it would

be with organisms with MICs of eight where we might expect there to be some decrease either in bacteriologic or clinical response.

And I think that you'll find as the clinical data is presented later is that that data actually agrees with the predictions.

Thank you.

And I will then extend -- the next presentation will be by Dr. Marchant.

DR. MARCHANT: Good morning. I'm going to talk this morning about scientific issues relating to measuring the efficacy of antibiotics and extend some of the issues that have already been raised by previous speakers this morning.

First of all, I'm going to have a couple of slides on overview, and then I'm going to consider two issues. What are the possible outcomes that we could use to measure efficacy of antibiotics in acute otitis media?

Well, first of all, symptomatic response is the obvious one. That is the one that is meaningful to the patient, the child, the parents. That's what they care most about.

The second one is otoscopic evidence of persistent infection, typically the opaque, bulging

eardrum. While this clinical finding is validated as an initial finding to diagnose a high probability of bacterial infection, it has on its own not been validated as an outcome in clinical trials of otitis media.

Middle effusion is an outcome that can be measured objectively. It's going to lead to decreased hearing in the child. Dr. Giebink also mentioned that it might go on and lead to problems with school performance and language acquisition. However, those issues remain in scientific dispute today, and we can't with confidence say that that's such a meaningful outcome.

And then commonly we have compound outcomes involving many of these. Then there is the bacteriologic outcome, the eradication of organisms.

The second issue to consider is the timing of measuring these outcomes. The symptomatic outcome has often been measured early on at 48 to 72 hours. The bacteriologic outcome and its clinical correlates have been measured typically on days four to six.

Then there's an end of therapy visit potentially, and then there's outcomes later on that are used presumably because there is a belief that events after stopping therapy are related to failure

to deal with the organism during therapy, and I will address that issue.

So the first issue that I'd like to talk about -- next slide -- is the relationship between symptomatic response and elimination of bacterial from the middle ear.

Next slide.

This, Dr. Giebink kindly showed you this data earlier. I'd like to make a couple of points. The first one, this is from the double tap studies that we did in Cleveland where we either eradicated the organism or didn't, and we looked at the clinical response in terms of fever, irritability, and ear ache at the time of the second tap, and this was done by nurses who were blind to whether the bacteria was there or not. They didn't know that.

And if you look at clinical success, you see that nice correspondence when you eradicate the organism, but some fail despite that.

And when the organism persists, there are still a lot of patients that appear to be better.

The other important thing that I'd like to draw your attention to is that this is a significant relationship. There is a significant correlation between the two events, bacterial eradication and

This is the double tap study with bacteriologic diagnosis and bacteriologic outcome, and you can see the sample sizes are small.

If then you look at the cases that are bacterial cases by tympanocentesis and then you evaluate the outcome clinically, up here you need great sample sizes.

And then if you look at clinical studies only with no tympanocentesis, the sample sizes get very high. You'll notice on this vertical axis these sample sizes are really not within, most of them, achievable sample sizes in clinical trials.

Let me show this same data on the next slide with a different, more realistic access, and if you'd quickly put up the other three graphs, you can see that the clinical outcomes are off the chart at 2,000 patient trial -- that's an n of two -- even for drugs that are really quite mediocre in terms of bacteriologic efficacy.

Next slide.

The data that I showed you from Cleveland have since been validated yet again in a second study by Dr. Dagan. He used a slightly different set of definitions a clinical scoring system based both on symptoms and signs.

Again, these are determined at the time of the second tap, and if you eradicate the organism, the green, the cures here, are in his study 97 percent, very high, but if you fail to eradicate the organism, your rate of clinical failure is much higher.

So he, again, is validating that the clinical outcome and the bacteriologic outcome agree, the bacteriologic outcome now validated for a second time.

Next slide.

So now let's go back and focus. What about these cases where we had persistence of the organism, but clinical success? This means there is a lag phase in terms of bacteriologic eradication or perhaps other factors determine the patient feeling better or the parent perceiving the patient to be better.

And then let's focus on these cases where the organism has been eliminated, but the patient is not better, and Dr. Giebink has already alluded to this this morning.

Next slide.

This shows you a study done in clinical practice when patients come in and they receive a tympanocentesis when they have failed to respond to

therapy, and this middle column shows you that half of the time or better than that there are no bacteria in the ear.

The drugs have presumably done their job, but the patient is not better.

Next slide.

As Dr. Giebink said, this is also a viral disease. This is a study from Scandinavia where they compare newly diagnosed otitis media with cases that are failing antibiotic therapy after 48 hours, and they look for viruses in the nasopharynx, in the middle ear, and they find that the rate of viral isolation or viral detection -- this is mostly antigen detection -- is higher in those that are failing therapy, suggesting that the viral etiology is contributing to these failures.

Next slide.

I'd like now to shift to an issue about the timing of measuring the clinical response, in this case the clinical symptoms. This is a randomized placebo controlled trial done in Copenhagen where they compared penicillin and placebo. As it turns out, their patients were all older, between ages three and seven, and they were asked to fill out a pain score.

You can see here that on the second day

there's a statistically significant difference in favor of antibiotic therapy, despite the fact that the patients in the placebo group took more aspirin and more acetaminophen for relief of their pain.

But you'll also notice that if you tried to measure this outcome too early or on day four or five, too late, you have no chance of finding a difference between a placebo and a drug.

So there is a period when your ability to measure this outcome is going to be there, and later on it's going to be too late. Everybody is going to look better whether there was a drug or not, or whether there was a drug that did its job and eliminated bacteria or one that didn't.

Because these patients are older in this study, this curve has probably shifted somewhat to the right.

Next slide.

We know that young patients are more likely to fail bacteriologically. This is, again, data from our work in Cleveland where the patients with bacteriologic success are older on average than those that are failing therapy.

Next slide.

Here's data from the Kaleida study in

Pittsburgh, again, looking at age, and whether you're put on amoxicillin or put on placebo, the younger patients do less well than the older patients in terms of initial symptomatic failure.

Next slide.

So this is a diagram which I hope will be helpful in thinking about this. If we view this as the time of the onset of treatment and this the degree of the patient's symptoms, they may get worse or get better as time goes on, with this bar moving to the left or moving to the right.

And I've used arrows with the idea that we vaguely remember from taking physics courses in high school where vectors may have been arrowed. The longer the arrow, the greater the force, if you will.

The important thing here is there's many factors. The ones that we're evaluating here with antibiotic therapy are bacterial infection and antibiotic therapy, but there's the viral infection issue, the host response, the persistent inflammatory response that Dr. Giebink drew your attention to.

And while this is present, it's clear from the correlation between clinical and bacteriologic efficacy that at least you can measure this over and above these effects.

Also, on the bottom, there may be other factors that relate to symptomatic response. Psychological factors are well known to be present in patients in their response to symptoms, et cetera.

So what we're evaluating in otitis media is a complicated situation, and we're really focusing on only a couple of the forces involved, if you will, and so we can't expect to have tight correlations we have. We're lucky that we have correlations.

Next slide.

I'm now going to move on to a second question about the timing of the outcome and ask: are recurrences of acute otitis media after therapy failures of therapy?

Or in another related question: should outcomes after therapy be used in comparative trials of antibiotic therapy of otitis media?

Next slide.

Again, Dr. Giebink and I share the same slides, perhaps present them slightly differently. You've already seen this data in a different form.

This is the Kaleida-Pittsburgh study, which I would submit is the most carefully done placebo controlled trial of antibiotic therapy in acute otitis media. They had to divide their patients

into severe based on pain and fever criteria and nonsevere because they rightly, I think, felt they could not offer placebo to severe patients.

So patients in the severe group got either myringotomy or amoxicillin or both, and patients in the non-severe received placebo or amoxicillin.

The non-severe group were 78 percent of all the otitis seen in these Pittsburgh practices and at the children's hospital in Pittsburgh. So the non-severe group represents the majority.

Next slide.

I'd now like to focus on the outcomes, and again, DR. Giebink did show you this also, at least the first part of this. The amoxicillin group, the placebo group, large numbers, initial symptomatic failure measured at 24 to 72 hours, a significant difference.

You measure effusion. You find about a 15 percent difference at the end of therapy, and by the way, these are a 14-day course of amoxicillin or placebo here. So they're ending it at 14 days. So this is an end of therapy middle ear effusion by tympanometry or expert otoscopy, a 15 percent difference.

You'll notice by six weeks, four weeks

later, most of this difference here is washed out. There's now only a six percent difference. Why did that happen? Because of recurrences.

The recurrence rate in the amoxicillin group was the same as that in the placebo group. You should conclude that perhaps recurrences have little or nothing to do with amoxicillin or placebo. If you did a randomized trial of any phenomenon in biologic or clinical system and compared a factor versus no factor, measured an outcome and found the same number, you would conclude that there was no causal relationship between this factor that you're studying and the outcome that you looked at.

So now I'm going to explore this from a microbiologic point of view.

Next slide.

Again, to begin, I'm going to talk about data that we assembled in Cleveland, and we did a study where we looked at early recurrences of otitis media in patients that were in antibiotic trials.

And first of all, the patients most likely to get recurrences, the only significant finding was if you had had many previous, three or more, episodes of otitis media before entering the trial, you were more likely to get otitis media afterwards, and that's

who got these clinical recurrences.

We did a tympanocentesis at the first episode and a tympanocentesis of the recurrences, and we looked at the organisms. For the pneumococci, we looked at capsular serotyping. For Haemophilus this is a 1980 study. We looked at the outer membrane protein profiles of Haemophilus influenzae and biochemical biotyping and beta-lactamase production.

For Moraxella, we were limited to beta-lactamase production as the only way to distinguish between one strain and another.

We asked how many are new episodes of infection with different species or strain and how many are relapses, and some were undefined because there was a sterile middle ear fluid either initially or on the second tap.

Next slide.

Let's zero in on, first of all, the relapses. There's a pneumococcus. We actually couldn't grow it. So we assumed it must be the same. Give the null hypothesis the benefit of the doubt.

Moraxella and H. flu. at one time, Moraxella the second, two more Moraxellas, and here's a real, genuine relapse. This is a child with a 6B pneumococcus both times and a Haemophilus isolate

that's beta-lactamase negative, the same biotype and same outer membrane protein profile.

So you have some true relapses, but only four of them.

Next slide.

They are outnumbered by the new infections, and you see the species changing. You see a pneumococcus, first at 14, then at 23F. You see down at the bottom here an H. flu. that's beta-lactamase negative both times, but when you do biotyping and the outer membrane protein electrophoresis, they are clearly different strains.

Overall then -- next slide -- a three-to-one ratio of new infections to relapses with the old bacteria, and these are all within 34 days of the initial diagnosis and, therefore, about 23 days of the end of therapy.

Since then, some five years later -- next slide -- Del Baccaro and colleagues did another study looking at this same issue. They looked at whether it was, again, new infections, shown in red, or relapses, shown in blue, and I have now put these out on a time line of days post therapy for you to look at.

Again, the numbers are small, but new infections outnumber relapses.

This is the end of antibiotic therapy. I submit that in these early days after stopping therapy, that with the drugs that we have that have relatively short half-lives, that the serum concentrations are way below anything that would inhibit bacteria out here, and we can't really expect our antibiotics to prevent infections with new strains when the antibiotics have been cleared from the circulation and presumably from the middle ear.

Next slide.

Since then, more recently ICCAC 2000, Eugene Leibowitz and Ron Dagan have done a series. Again, now they're in the molecular age, and they're doing pulse field gel electrophoresis, as well as serotyping for the pneumococci.

Again, I've used the red to indicate new infection, the blue to indicate relapses. Even in the first week after therapy new infections outnumber relapses.

So most of the events then occurring are new bacterial events that we should not expect antibiotic therapy to have much effect on.

Next slide.

So by way of review, the symptomatic response is the one that the parents and the patients

care about, but the sample sizes are astronomical to assess that outcome in comparative trials.

The otoscopic appearance needs to be validated as an outcome. Middle effusion I've already mentioned.

Eradication of bacteria from the ear is attractive for two reasons. Number one, it has been validated to correlate with clinical symptoms twice, two separate studies.

Number two, it is biologically meaningful. The accomplished microbiologists in the room, Drs. Craig and Soreth, spend their time thinking about how you're going to get concentrations of drug to inhibit and kill organisms at the site of infection, and it's a biologically valid concept, as well as a clinically validated concept.

Next slide.

Now, to review some of the timing of outcomes, certainly the symptomatic outcome is probably optimally measured at some time like this, but maybe at least early. If you try to do it at ten days, it may be all over. The horse may be out of the barn.

The bacteriologic outcome has traditionally been done at day four and six. The

range has been two to seven, if you go back to Dr. Howie's study. There are no data for the bacteriologic outcome at the end of therapy. So anybody that thinks it's a good outcome first needs some data to show that it's a good outcome because all of the data available is during this time.

However, the end of therapy outcome seems to be clearly preferable to this outcome later on, which the term has been used "test of cure," and I'm sure that term will be used later today.

But because most of the events here are, in fact, new bacteriologic events, because the placebo control trial shows that later outcomes really are not responsive to antibiotics in the first place, this outcome does not seem to have much validity.

So I salute Dr. Soreth and her colleagues for reopening the issues of design of clinical trials and some of the issues that have been discussed earlier this morning, and I urge in that process that there be careful review of the scientific data, whether there's data there to support an outcome or whether there's no data, and whether that scientific data is valid scientific data.

Thank you very much for your attention.

DR. WYNNE: Good morning. I'm Brian

Wynne. I'm an Associate Director of Clinical Research for the Antibiotics Division of GlaxoSmithKline.

And my role this morning is to present the clinical trial data that evaluates the efficacy of Augmentin ES and bacteriologic and clinical efficacy in the study of acute otitis media.

My goal this morning is to present these objectives. Briefly we'll discuss the rationale and background and the study design; will then present the results.

I'm particularly keen on those patients with penicillin resistant Streptococcus pneumoniae, also those patients with amoxi. clav. MIC of four, and finally patients with beta-lactamase producing organisms.

We'll briefly touch on the safety you've seen in the clinical trials, and then we'll discuss some overall conclusions.

What we'll see today is that Augmentin ES, a 14 to one formulation, for the use of acute otitis media demonstrated excellent bacteriologic and clinical efficacy against penicillin resistant Streptococcus pneumoniae.

We'll see that there was efficacy against those Streptococcus pneumoniae with amoxi.-clav. MICs

up to and including four micrograms per mL.

We'll see clinical and biological efficacy against beta-lactamase producing organisms, in particular, Haemophilus influenzae, Moraxella catarrhalis. They're so important in respiratory tract infections.

And finally, we'll see that it maintains the well known and acceptable safety profile of the currently marketed formulation.

Why was Augmentin ES developed? I think the earlier speakers have touched on this. Increasing S. pneumoniae worldwide, not just to penicillin, but to all classes of available pediatric treatment.

Few choices are available for the empiric pediatric treatments of penicillin resistant Streptococcus pneumoniae. We had a product with a well known safety profile and 16-plus years of experience in the United States market. Physicians and parents were experienced with it.

And we noticed in a lot of the literature that physicians are already calling for enhanced amoxicillin component with clavulanic acid in the treatment of infections. We had seen it in CDC guideline recommendations and many health plans. They were recommending their own physicians to go back with

an enhanced formula of amoxicillin in treatment failures or recurrent otitis media.

And we had seen that in many literature sources this was a dosage that would be well utilized by the pediatric community.

The rationale for 14 to one. We kept the one because clavulanic acid at 6.5 milligram per kilogram dose twice per day has been proven efficacious, and is a beta-lactamase inhibiting dosage. So that was kept the same.

The 14. The choice of 90 milligram per kilogram per day of amoxicillin in these patients, based on PK/PD data as already discussed by Dr. Craig.

Further, we'd seen some in vivo animal data, as again presented by Dr. Craig, and we had had some early clinical pharmacokinetic data as we saw, again, verified in Study 574 in pediatric patients.

So a little bit of background on the study. In response to discussions with the agency, GSK designed a clinical trial titled noncomparative multi-center study to demonstrate the bacteriologic efficacy of Augmentin ES in the treatment of acute otitis media due to Streptococcus pneumoniae.

Study designs and objectives, including the primary efficacy parameter of on therapy

bacteriologic response, were discussed with the agency before initiation.

A brief overview of the design as already described. It was a noncomparative multi-center conducted primarily in the United States and Israel and also three sites in Central America. The Augmentin ES was dosed at 90 milligram per kilogram per day.

They were all bacteriologically confirmed cases of acute otitis media in the protocol population. As opposed to many studies for the approvability of this indication, we only took those patients with bacteriologically proven cases of acute otitis media.

We performed repeat tympanocentesis on day four to six for all patients who grew Strep. pneumoniae at the initial tympanocentesis, proving bacteriologic eradication on day four to six.

We also tapped all other isolates who had clinical failure at the time of failure. However, three sites did repeat tympanocentesis on day four to six for all patients who had any pathogen at the initial tympanocentesis.

Next slide, please.

The primary objective of this study was

the evaluation of bacteriologic efficacy of Streptococcus pneumoniae. In particular, we were looking at those cases of penicillin resistant Streptococcus pneumoniae and those cases the amoxicillin-clavulanic acid MICs of four. This was the stated primary objective from the beginning of our study.

Enrollment target. We arrived at approximately 700 pediatric patients in the planned enrollment. That was derived by realizing that approximately one out of 50 patients would have an amoxi.-clav. MIC of around four. We based that on prior clinical trial data and also some surveillance data.

We were also, in later consultation with the agency, advised to look for at least 20 pediatric patients with PRSP.

Next slide, please.

In order to achieve these goals, we looked at enriched study populations. This was touched on earlier by both Dr. Giebink and Dr. Soreth, and the idea was we looked at younger children, an age range of three to 50 months.

We only excluded systemic antibiotics if they are within three days of enrollment. Typically

it's a seven-day, sometimes 30-day washout period. Our patients could be on antibiotics up to three days.

We allowed prophylaxis up to the time of enrollment in the study. There was no exclusion for recurrent or recent acute otitis media, again, very common in a lot of clinical trials. We did not do that.

And finally, we had no inclusion in our bacteriologic population for those who had resistant bacteria at time of initial tympanocentesis, again, a study technique that has been used in many other trials where they only evaluated those agents -- I mean those bacteria that were not considered resistant to the agent under study not undertaken here.

No review of the study plan. A preliminary visit of course with initial tympanocentesis for all enrollees. An on therapy visit from days four to six.

It was our opportunity to evaluate the patients and to validate bacteriologic efficacy on days four to six. All Streptococcus pneumoniae had repeat tympanocentesis at that time.

Again, we scheduled those who had continued to improve for an end of therapy visit. Again, we scheduled those who continued to improve for

that and you realize that there was 41 penicillin resistant Streptococcus pneumoniae isolated, which represented our intent to treat population, and 80 percent of those were protocol evaluable.

Two things to note. One is that 26 percent of the Streptococcus pneumoniae isolated in this clinical trial were penicillin resistant, MIC greater than or equal to two, highlighting the contemporary need for an agent designed to meet this need in clinical practice.

And the other thing is 41 PRSP in a prospective trial is the largest that we know collection of penicillin resistant Streptococcus pneumoniae evaluated in pediatric patients.

The other bacteriology in the study, what one would expect: predominantly Haemophilus influenzae, some Moraxella catarrhalis, and 21 percent of the taps grew multiple pathogens, again, a number very consistent with prior clinical trials.

Next slide.

Primary efficacy parameter. Again, bacteriologic response on therapy, days four to six in patients with Streptococcus pneumoniae. We had secondary parameters of clinical response as determined by the primary investigator at the end of

therapy visit in patients with Streptococcus pneumoniae.

Our key clinical endpoint and our key clinical population, those Streptococcus pneumoniae.

We also looked at bacteriologic and clinical response in patients who grew other pathogenic bacterial, and we looked at clinical response as determined by the investigator between two and two and a half weeks after the end of therapy.

So what were our results? What was the efficacy in the patients with Streptococcus pneumoniae?

And the answer is it was high bacteriologic success rate. Ninety-eight percent of all Streptococcus pneumoniae were eradicated at the on therapy tap.

Next slide.

More importantly, those patients with penicillin resistant Streptococcus pneumoniae, 94 percent eradication in the protocol population, 93 percent in the intent to treat eradication and repeat tympanocentesis on day four to six, proven in vivo bacteriologic eradication in children treated for acute otitis media with Augmentin ES.

Next slide.

We saw it across the range of susceptibility patterns for Streptococcus pneumoniae. One looks at penicillin susceptible on the left, intermediate in the middle, and resistant on the right, consistently strong bacteriologic eradication of Streptococcus pneumoniae in children treated with Augmentin ES.

How do these data compare to the known natural history of acute otitis media? As discussed by Dr. Marchant, not a whole lot is known about the natural history of PRSP clinically. We do, however, now a lot about or a fair amount about the natural bacteriologic history of acute otitis media.

This was developed in the 1970s and continued to the 1980s by Dr. Virgil Howie and colleagues. And what we've seen is Streptococcus pneumoniae is the least likely organism to spontaneously resolve.

Through a series of studies that concluded that Streptococcus pneumoniae had a spontaneous eradication rate between days three and seven of approximately 20 percent versus perhaps 50 to 80 percent for other pathogens.

I'll call attention to the fact that if the natural history is a 20 to 30 percent eradication

in untreated patients between day three and seven, we have a 93 percent eradication rate in penicillin resistant Streptococcus pneumoniae at day four to six, clearly different than the natural history of this disease.

Bacteriologic efficacy is predictive of clinical effect. Efficacy, again, is discussed by Dr. Marchant.

Next slide, please.

The clinical success rate continued in this product across the penicillin MICs.

Next slide, please.

How does the end of therapy clinical efficacy of Augmentin ES compare to currently approved drugs?

I'll beg the committee's tolerance for these next series of slides. They are build slides, and so I'll describe them as I go through.

If we look at the clinical success rate at the end of therapy for Augmentin ES for all pathogens, we have a 91 percent clinical success rate between days two and six after completion of therapy in those children who grew a pathogen at entrance, not all screened; bacteriologically proven acute otitis media.

Next slide.

In looking at other studies where they used entrance bacteriology, you've seen 84 percent into therapy clinical success for a zithromax study and an 87 percent clinical success for a ceftriaxone study.

Next slide.

If one looked at only those studies that evaluated the Streptococcus pneumoniae, one sees 89 percent clinical success in our Streptococcus pneumoniae population and 84 percent in a ceftriaxone study.

I need to highlight at this time, however, that the average age of the zithromax enrollees was four years. Our average age is 18 months. We've already seen that the natural clinical history of those older children has much higher rates of spontaneous resolution in clinical success.

In the rocephin study, the average age was 30 months.

How does our success in the most highly resistant organisms at the end of therapy window look? And here's the data.

Eighty-two percent clinical success in penicillin resistant Streptococcus pneumoniae patients. The only other study to evaluate the

penicillin resistant subset was, again, a ceftriaxone study where they had a 65 percent eradication of their penicillin or not eradication -- excuse me -- clinical success at the end of therapy window in the penicillin resistant Streptococcus pneumoniae population.

Again, to put the perspective into that study also as that their average age was 30 months. We have 18 months. We evaluated 41 penicillin resistant Streptococcus pneumoniae. That is the biggest group ever evaluated in this indication at this time point, and we have excellent success.

Next slide.

In looking at clinical studies at this time point -- next slide, please -- again, you go back to our baseline slide. Ninety-one percent clinical success, at this time point, most closely reflects the bacteriologic eradication.

Next slide, please.

Other studies that have looked at this time point. A zithromax study number one, a clinical only study. Average age of enrollees was six, and they have an 87 -- excuse me -- 88 end of therapy success rate.

Rocephin study one, 74 percent. The average age of enrollment was four years.

If you look at study number two rocephin, the comparator was TMP sulfa and themselves. You see a 54 and 60.

That's a tricky study to compare with because there was some reassignment done by the review team, but it looked for those who had only proven tympanometric and reflectometry measurements, and there was also some reassignment from patients who had experienced a second dose of ceftriaxone.

However, the final concluding numbers as agreed upon at that time in that study was 54 percent and 60, and while there seems to be somewhat of a disconnect between the earlier rocephin study, I need to point out that there was an average age of 30 months in study number one and 17 months in study number two.

What we've seen in studies that look at younger children, it is outstanding to see a clinical success rate of 91 percent at the end of therapy.

Again, our Streptococcus pneumoniae, 89 percent clinical success at the end of therapy.

Next slide, please.

Eighty-two percent clinical success at the end of therapy in our penicillin resistant Streptococcus pneumoniae subset.

Dr. Marchant has already addressed what happens to clinical efficacy after the therapy stops. You've seen this slide. I apologize, but basically what Dr. Carlin and her group study showed in 1987 in Cleveland was that about 14 percent of children who had clinical relapse within 28 days of initiating therapy, had relapse of the same organism, and other than that they either had a dry tap; they had symptoms, but none of the bacterial persisting, or the had a new infection with a different pathogen.

Next slide.

We plotted this out for our own trial. What did we see? And what we see, again, almost predicting what one would see with the Marchant phenomena, at the on therapy date, four to six, bacterial eradication, strong rates of bacteriologic eradication.

If one goes to day 12 to 15, the second time point, that's our end of therapy clinical evaluation. One sees a slightly lower success rate, as would be predicted in the Polyanna phenomenon.

However, if one carries this out to a day 25 to 28 window at the test of cure, one sees regardless of the pathogen, regardless of successful eradication and successful improvement at the end of

therapy, you see clinical symptomatic recurrence.

We do know, however, that the biggest drops were noted in Moraxella catarrhalis and the PRSP subset.

Next slide.

So what we've learned at this point is that reinfection and recurrence in AOM patients is common in the weeks following treatment, but we wanted to see what factors may have contributed to the higher rates of reinfection or lower clinical success rate observed at the test of cure for that subset of patients with PRSP.

We searched the literature, and we found that when they took evaluation for what are the common reasons for recurrent AOM and what are the common reasons for carrying PRSP or even having a proven infection involving PRSP, they've defined the same population.

What we see, it's an age related phenomenon. Children or siblings, children in higher day care attendance, children with a history of recurring acute otitis media, these are otitis prone children.

We also saw a seasonal correlation. There are other factors that predict recurrence.

Next slide.

Part of this though in correlation with our study, study 539. Indeed, if you look at the patients who had penicillin resistance in our population versus those how had a penicillin nonresistant, either intermediate or susceptible Streptococcus pneumoniae, they were statistically younger, statistically higher prior history of AOM, statistically had received more antibiotics in the prior three months. While not statistically significant, but all trending in that same risk category was day care attendance, male gender, and siblings, all known risk factors, recurrent otitis media.

We also looked, and it's not on this slide, at a history of AOM in the last 30 days before enrollment. Statistically higher in the PRSP subset.

While we believe that the end of therapy evaluation time point is clearly the most appropriate in evaluation of this drug, we did look at the test of care clinical efficacy of Augmentin ES, and we were curious to see how this compared to other agents.

And I apologize and ask for your indulgence again. It's another series of build graphs.

When you look at all of our pathogens at the test of cure window, 74 percent clinical success at the test of cure.

Next slide, please.

If you look at studies that did baseline bacteriology and followed those patients out, what is their success at the test of cure window? You see a 70 percent in the zithromax study, and in an omnicef study 65 and 64 for the two arms.

The amazing thing about these studies, the zithromax study had an average age of four, and the omnicef study was 33 months. We had an average age of 18 months.

If you look at the omnicef study two, they had a 59 percent success. That was a slightly younger study. It was 27 months was the average age.

Next slide, please.

If you look at those studies and just evaluate the Streptococcus pneumoniae subset, the organism least likely to spontaneously eradicate and the one most common to cause otitis media, you see a 73 percent continued success rate at the test of cure window in those patients treated with Augmentin ES.

If you look at the omnicef second study, the one with the 27 month average age, they had a 57

percent prolonged success rate at the test of cure window.

Next slide, please.

If you look at those who went on to -- what are high risk factors? If they didn't do PRSP per se and they looked at other high risk factors, you see that the omnicef study evaluated those patients who were under age two, and what you see at the test of cure window in those clinically evaluated patients less than two years of age. They had a 49 and 48 percent continued success rate of the test of cure window compared to a 74 percent success rate for Augmentin ES at the test of cure window in a highly select population, young, history of recurrent otitis media, high day care attendance, excellent clinical activity in the penicillin -- excuse me -- in the Augmentin ES patients.

If you go to the next slide, we'll look at the PRSP subset. Only one study has made that evaluation at that time point before, again, the ceftriaxone study.

Thirty-seven percent tested cure clinical success compared to our 53 percent penicillin resistant clinical success. Two things to note in that. The ceftriaxone study was a 37 percent PRSP.

They ruled out recurrent otitis media patients at enrollment, already selecting out those patients who are prone for recurrence.

The other thing in the zithromax bacteriology study to note is they also eliminated those patients who had zithromycin resistant pathogens at time of initial tympanocentesis, as did the omnicef studies. We did not do that.

How do we look compared to clinical studies? No baseline bacteriology, but they just evaluated clinical success of the test of cure window.

Next slide, please.

Again, 74 percent, all pathogens, not all comers; all those with proven bacteriologic AOM.

Next slide, please.

These other studies compared all comers' clinical signs and symptoms, which means they probably enrolled on odds 25 to 30 percent of those patients with acute otitis media symptomatology, but not necessarily bacteriologically mediated otitis media symptomatology.

And, indeed, one sees strong, top of the line success in the Augmentin ES population.

Next slide.

If you look at the Streptococcus

pneumoniae Augmentin ES population, 73 percent success. Remember 27 percent or 26 percent of our Streptococcus pneumoniae were penicillin resistant Streptococcus pneumoniae, and still at the leading end of success at this time point in clinical trials.

Next slide.

If you look at those with PRSP, 53 percent. While there is a drop down and we feel this drop down is from the risk factors, still clearly within the success range for all other studies when they merely evaluated clinical input and clinical output and not taking into account those patients with only bacteriologically proven acute otitis media.

The conclusion from our clinical trial. We feel that excellent bacteriologic and clinical efficacy in acute otitis media caused by Streptococcus pneumoniae, including those cases caused by penicillin resistant Streptococcus pneumoniae was demonstrated in our clinical program.

Next I'd like to discuss briefly the efficacy seen in those patients with amoxi.-clav. MICs of four.

Next slide, please.

This study was designed with two time points of analysis,a nd the first time point was in

November of 1999. That is the data set that the agency has had full time to review and has been the basis of most of the discussion.

At that time 521 patients have been enrolled. Four hundred and forty-one PRSP isolates have been obtained.

At that time there were four -- excuse me -- three isolates of the amoxi.-clav. MIC of four and six isolates of the amoxi.-clav. MIC of eight isolates.

Next slide, please.

And what is our success rate bacteriologically? Well, the numbers are small. Once these continued bacteriologic success up to and including those isolates with an amoxi.-clav. MIC of four. It's all about predicting the model by Dr. Craig in the animal studies.

This drug was designed to keep in mind those patients with isolates up to and including an MIC of four, and indeed, the bacteriologic eradication followed that.

Next slide, please.

As did the clinical success at the end of therapy window.

Next slide, please.

As did the clinical success at the test of cure window.

Next slide, please.

Those investigators who had provided us with resistant Streptococcus pneumoniae were encouraged to continue enrolling until June of 2000 to get through the rest of the respiratory season, to see if we could find more isolates with amoxi.-clav. MICs of four.

Next slide, please.

What one sees in the yellow is the June analysis, and there are two more isolates at each MIC, an MIC of four and an MIC of eight isolated in that time period.

Next slide, please.

And what we see is continued, strong, bacteriologic eradication up to and including isolates with an amoxi.-clav. MIC of four. The one failure in the intent to treat population with an MIC of four was not an known failure. That was a patient who presented for initial tympanocentesis and was lost to follow-up despite the investigator's attempts to recontact.

There was no provide bacteriologic failures with an amoxi.-clav. MIC of four in this